## REMARKS

Claims 1-27 are pending. Claim 26 is canceled herewith. Claims 28-47 are added. Support for these amendments appears throughout the specification and claims as filed, including at pages 2 to 9 of the specification. No new matter is introduced by these amendments. Applicants make these amendments in order to expedite prosecution of these claims. Applicants make such amendments without prejudice to pursuing the originally presented or cancelled subject matter in a later application claiming benefit of this application, and particularly without prejudice to determination of equivalents of subject matter of this application or any later application claiming benefit of this application.

### Priority Claim

Applicants reiterate their priority claim under 35 U.S.C. 119 (a-d) based upon Swedish application no. 0003810-9, filed October 20, 2000. As October 20, 2001 was a Saturday, the filing of the application on Monday, October 22, 2001, with priority benefit to Swedish application 0003810-9 is proper. See, MPEP 201.13. Applicants respectfully request acknowledgement of this priority claim.

### Rejection under 35 U.S.C. 112, second paragraph

Claims 24 and 25 are rejected as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter "a disease mediated by the serotonin-related 5-$HT_6$ receptor". It is alleged that one of ordinary skill in the art would not appreciate the disorders mediated by the serotonin-related 5-$HT_6$ receptor. Applicants disagree for the reasons set forth below.

Applicants submit that the phrase "a disease mediated by the serotonin-related 5-$HT_6$ receptor" means precisely, and literally, just that; a disease in which the 5-$HT_6$ receptor is involved in the disease process. Applicants also submit that one of ordinary skill in the art would appreciate the meaning of the phrase. Applicants note that a cited reference, U.S. Patent 6,251,893 ("Maddaford"), recites "...CNS conditions wherein a 5-$HT_6$ antagonist is indicated, for example, for the treatment or prevention of central nervous system disturbances such as

psychosis, schizophrenia, manic depression, depression, neurological disturbances, memory disturbances, Parkinsonism, amylotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease." Maddaford, Column 2, lines 26-33. Moreover, one need only peruse references in the field, such as A.J. Robichaud et al., *Annual Reports in Medicinal Chemistry*, D. Robertson, ed., volume 35, pages 11 and 16-17, Academic Press (2000) ("Robichaud"); A. Meneses, 5-HT system and cognition *Neurosci. Biobehav. Pharm.* (1999) 23, 1111-1125; D.C. Roger, T.L. Robinson, C.A. Quilter, A.J. Hunter, C. Routledge, J.J. Hagan, Cognitive enhancement effect of selective 5-$HT_6$ antagonist SB 271046 *Br. J. Pharmac.* (1999) 17, 22P; and Hirst, W. D. 5-$HT_6$ receptor and clinical possibilities, S12.2 *Neuroscience in Orlando* (Oct 31-Nov 10, 2002) (attached), for example, which in combination provide correlation of various 5-$HT_6$ receptor activity with function and disease (e.g., memory and cognition disorders, ADHD, schizophrenia, Parkinson's disease and depression). Thus, Applicants submit that the phrase "a disease mediated by the serotonin-related 5-$HT_6$ receptor" is definite, and request withdrawal of this rejection.

Claim 27 is rejected as indefinite with respect to the phrase "a CNS disorder". Applicants disagree. Applicants submit that one of ordinary skill in the art would appreciate the meaning of the phrase. Again, Maddaford recites "CNS conditions", thus indicating that one of ordinary skill would appreciate the meaning of the phrase. Moreover, Applicants submit herewith a copy of M. Williams et al., *Annual Reports in Medicinal Chemistry*, D. Robertson, ed., volume 36, pages 1-5, Academic Press (2001) ("Williams"), which delineates "CNS" or central nervous system disorders, including those listed in Tables 1 and 2 therein. See, Williams at pages 3 and 5, respectively. Applicants submit that Maddaford and Williams are merely two examples of the many resources available that provide indicia that one of ordinary skill in the art would appreciate the phrase "CNS disorder". Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. 112, first paragraph

Claims 24-27 are rejected because the specification, while enabling for treating specific diseases, allegedly does not provide enablement for preventing diseases. Applicants disagree with the allegation, however, as claims 24-25 (and claim 27 dependent thereon) are amended to

no longer recite "prophylaxis", and claim 26 is canceled, the rejection is moot. Applicants make such amendment in order to expedite prosecution of the application and without prejudice to pursuing the cancelled subject matter in a later application claiming benefit of this application.

Rejection under 35 U.S.C. 102(b)

Claims 1, 2, 4, and 11-13 are rejected as allegedly anticipated by Illi (Synthesis), claims 1-3, 5, 11, 12, and 14 are rejected in view of Nyasse (Journal of Organic Chemistry), claims 1, 3, 6-9, 11, 12, 15 and 16 are rejected in view of Goulaouic-DuBois (Journal of Organic Chemistry), and claims 1, 2, 4, 11-13, and 22 are rejected in view of Artico (WO 96/33171) . In the Action, it is alleged that each discloses one or multiple compounds that anticipate the delineated claims. Applicants note that all compounds cited in the Action and disclosed in these references are indolyl-derivatives having no substituents on the aromatic six-membered ring of the indolyl group. Applicants' claims, as amended, now recite compounds that must have at least one substituent on the aromatic six-membered ring of the indolyl group. As such, the cited references do not anticipate Applicants' claims as amended. Applicants respectfully request withdrawal of this rejection.

Allowable Subject Matter

Applicants note that Claims 18 and 23 are allowed and that claims 10, 17, and 19-21 were objected to as being dependent upon a rejected base claim. Applicants now submit that these claims no longer depend on a rejected base claim and are thus in condition for allowance. Applicants also note that they disagree with the allegation in the Action that claims 1-5, 11-14, 18, and 23-25, in the form prior to amendments made herewith, are *per se* obvious in view of Maddaford (U.S. Patent 6, 251,893). Applicants' compounds require a hydrogen atom at the 3-position of the indolyl group, while Maddaford requires a bicyclic heterocyclyl group at the 3-position of the indolyl group. Thus, Applicants' compounds are distinct and distinguishable, both structurally as well as functionally from the Maddaford compounds. Maddaford does not provide any motivation to arrive at Applicants' compounds. Moreover, as pointed out by the Examiner, Maddaford is not enabling for the synthesis of Applicants' compounds. As such, Applicants submit that their compounds are not obvious in light of Maddaford.

Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that all claims be allowed. Enclosed is a check for excess claim fees. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 13425-052001.

Respectfully submitted,

Date: February 5, 2003

Jeffrey D. Hsi
Reg. No. 40,024

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Attorney's [redacted]ocket No.: 13425-052001 / 00382-US



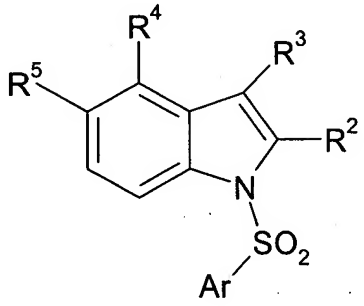
## Version with markings to show changes made

In the claims:

Claim 26 has been cancelled.

Claims 1, 2, 12-18, 22, 24 and 25 have been amended as follows:

--1 (Amended). A compound of formula (I):



(I)

wherein

Ar is

(1) phenyl,

(2) naphthyl,

(3) a 5- to 10-membered monocyclic or bicyclic heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting of oxygen, sulfur, or nitrogen, or

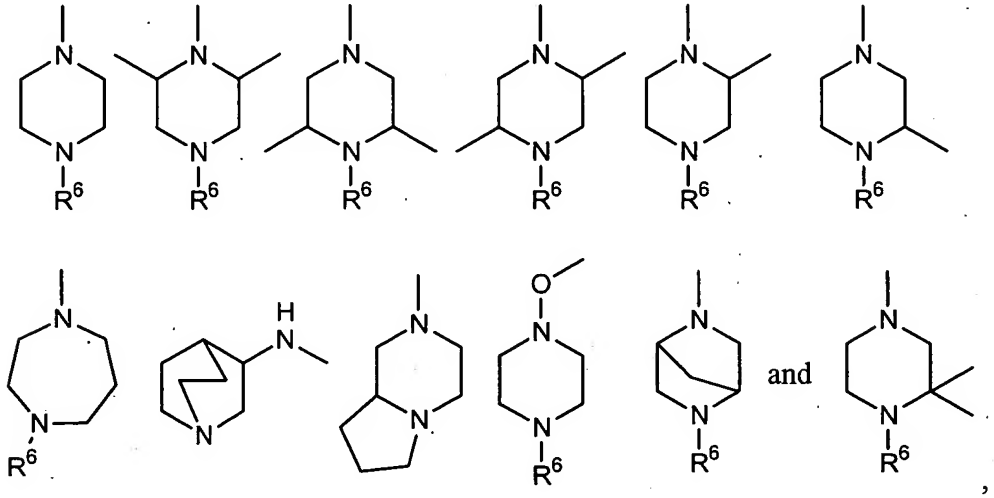
(4) -$R^9$-phenyl;

wherein the phenyl, naphthyl, or heterocyclic ring is optionally substituted with halogen, $C_{1-6}$ alkyl, $CF_3$, hydroxyl, $C_{1-6}$ alkoxyl, $OCF_3$, $COCF_3$, CN, $NO_2$, phenyloxy, phenyl, $C_{1-6}$ alkylsulfonyl, $C_{2-6}$ alkenyl, -$NR^7R^8$, $C_{1-6}$ alkylcarboxyl, formyl, -$C_{1-6}$ alkyl-NH-CO-phenyl, -$C_{1-6}$ alkyl-CO-NH-phenyl, -NH-CO-$C_{1-6}$ alkyl, -CO-$NR^7R^8$, or $SR^7$; wherein each of $R^7$ and $R^8$ is independently H or $C_{1-6}$ alkyl; and $R^9$ is $C_{1-6}$ alkyl or $C_{2-6}$ alkenyl, either of which is optionally substituted with phenyl or phenyloxy;

$R^2$ is H, phenyl, I, or $C_{1-6}$ alkyl;

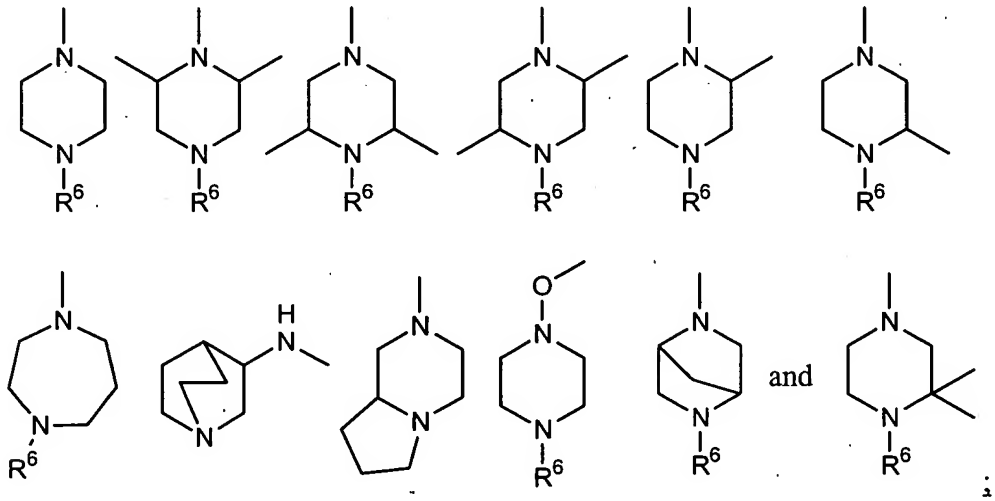
$R^3$ is H or 3-(1-azabicyclo[2.2.2]oct-2-en)yl;

$R^4$ is [H or is] selected from the group consisting of:




wherein $R^6$ is H, $C_{1-6}$ alkyl, or benzyl; and

$R^5$ is H, hydroxy, $C_{1-3}$ alkoxy, F, $NO_2$, $CF_3$, $OCF_3$, or is selected from the group consisting of:




or a pharmaceutically acceptable salt, hydrate, or stereoisomer thereof,

with the proviso that when $R^2$ is alkyl, $R^4$ is not H.

2 (Amended). The compound according to claim 1, wherein

Ar is

(1) phenyl that is unsubstituted or optionally mono- or poly-substituted with halogen, $C_{1-6}$ alkyl, $CF_3$, hydroxyl, $C_{1-6}$ alkoxyl, $OCF_3$, CN, $NO_2$, phenyloxyl, phenyl, alkylsulfonyl, $C_{1-6}$

alkenyl, $-NH_2$, $-NHR^7$, $-NR^7R^8$, $C_{1-6}$ alkylcarboxyl, formyl, $-NH-CO-C_{1-6}$ alkyl, $-CO-NR^7R^8$, or $SR^7$ wherein each of $R^7$ and $R^8$ is independently H or $C_{1-6}$ alkyl;

(2) 1-naphthyl or 2-naphthyl that is unsubstituted or optionally mono- or poly-substituted with halogen, $C_{1-6}$ alkyl, $CF_3$, hydroxyl, $C_{1-6}$ alkoxyl, $OCF_3$, CN, $NO_2$, phenyloxyl, phenyl, alkylsulfonyl, $C_{1-6}$ alkenyl, $-NH_2$, $-NHR^7$, $-NR^7R^8$, $C_{1-6}$ alkylcarboxyl, formyl, $-NH-CO-C_{1-6}$ alkyl, $-CO-NR^7R^8$, or $SR^7$ wherein each of $R^7$ and $R^8$ is independently H or $C_{1-6}$ alkyl;

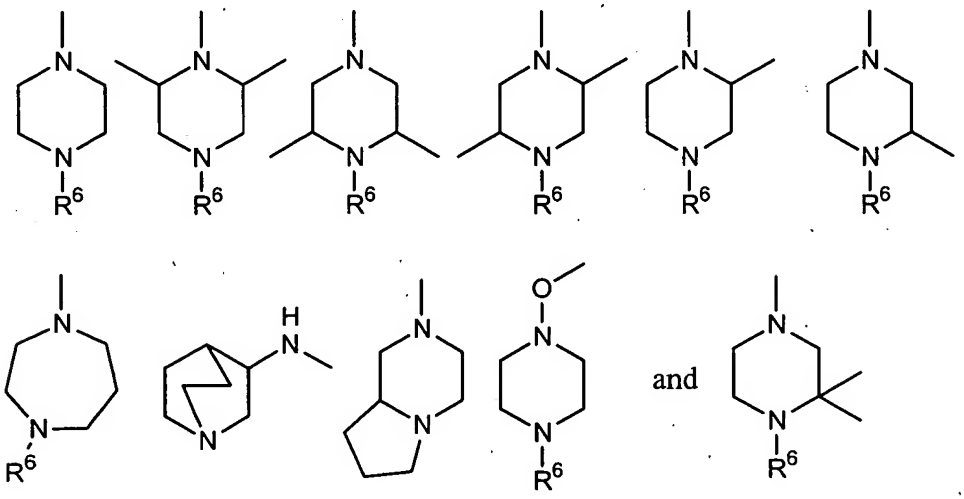
(3) cynnamoyl;

(4) benzyl;

(5) 1,1-diphenylethyl;

(6) a monocyclic or bicyclic heterocyclic ring selected from the group consisting of furyl, pyrrolyl, triazolyl, diazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl, pyrazinyl, thienyl, imidazolyl, pyrazolyl, indolyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, and benzoxadiazolyl, said heterocyclic ring being optionally mono- or di-substituted substituted with halogen or $C_{1-6}$ alkyl;

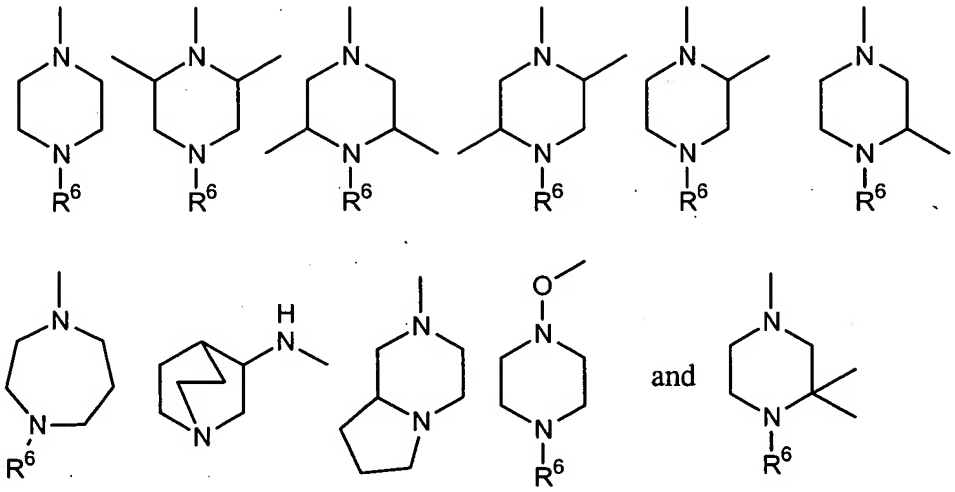
$R^4$ is [H or is ]selected from the group consisting of:



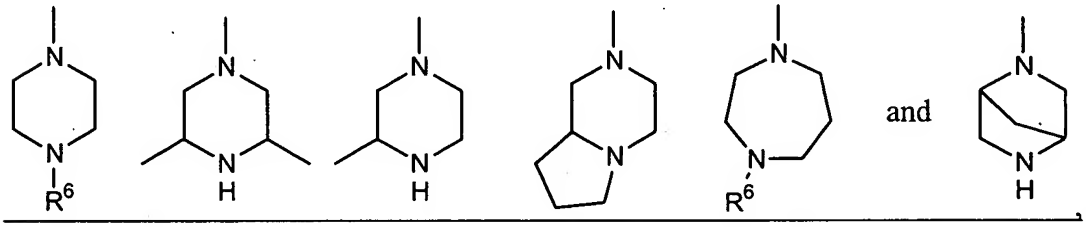

;

wherein $R^6$ is H, $C_{1-6}$ alkyl, or benzyl; and

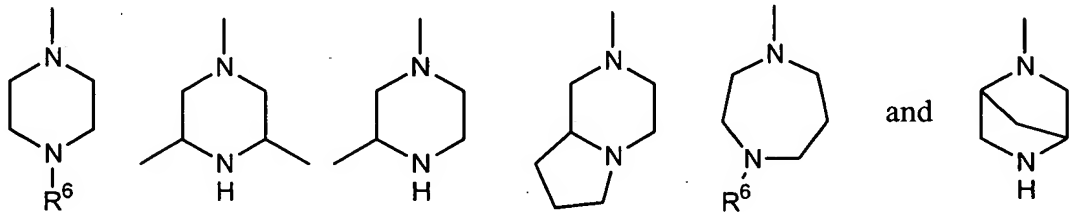
$R^5$ is H, hydroxy, $C_{1-3}$ alkoxy, F, $NO_2$, $CF_3$, $OCF_3$ or is selected from the group consisting of:




12 (Amended). A compound according to claim 1, wherein [each of] $R^4$ is independently a heterocyclic ring selected from the group consisting of:

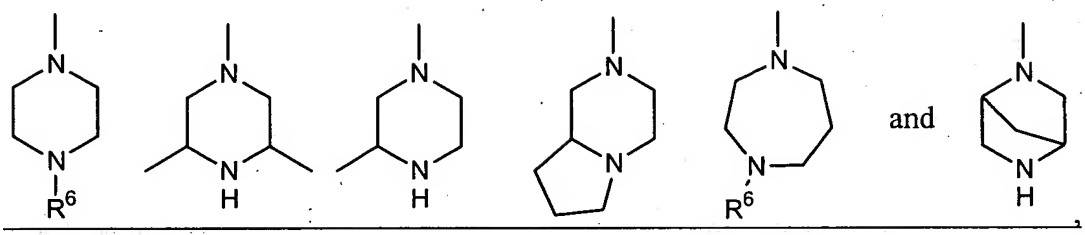



, and $R^5$ is independently H or a heterocyclic ring selected from the group consisting of:

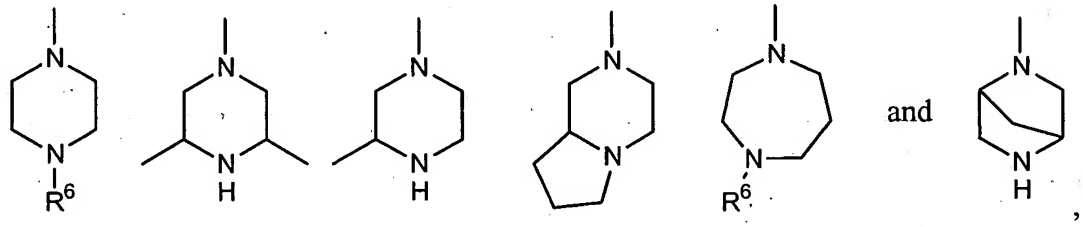



wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl.

13 (Amended). A compound according to claim 1, wherein Ar is phenyl, optionally substituted with F, Cl, Br, methyl, $CF_3$, $C_{1-4}$ alkoxyl, $OCF_3$, CN, $NO_2$, phenyloxy, phenyl, methylsulfonyl, or $-NR^7R^8$ where each of $R^7$ and $R^8$ is independently H or methyl; each of $R^2$ and $R^3$ is H; and [each of] $R^4$ is independently a heterocyclic ring selected from the group consisting of:



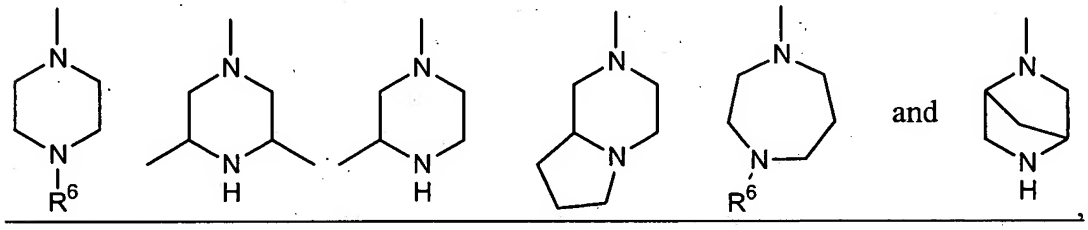

, and $R^5$ is independently H or a heterocyclic ring selected from the group consisting of:



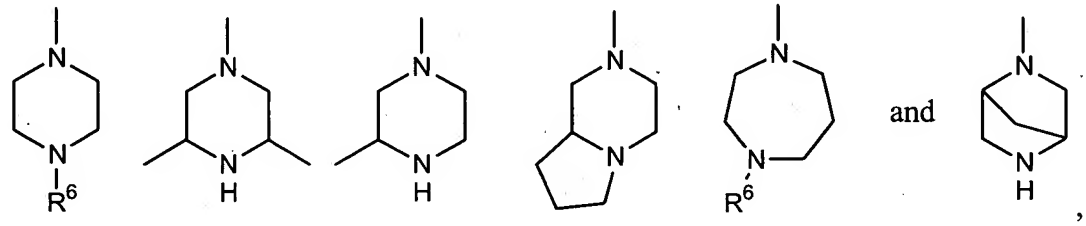

,

wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl.

14 (Amended). A compound according to claim 1, wherein Ar is 1-naphthyl or 2-naphthyl, each of which is optionally substituted with F, Cl, Br, methyl, $CF_3$, $C_{1-4}$ alkoxyl, $OCF_3$, CN, $NO_2$, phenyloxy, phenyl, methylsulfonyl, or $-NR^7R^8$, where each of $R^7$ and $R^8$ is independently H or methyl; each of $R^2$ and $R^3$ is H; and [each of] $R^4$ <u>is independently a heterocyclic ring selected from the group consisting of:</u>



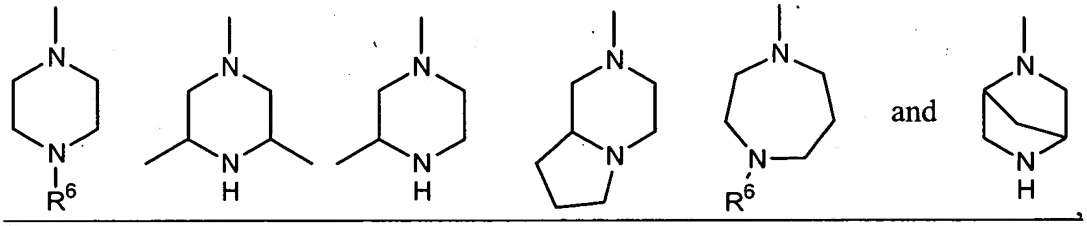

, and $R^5$ is independently H or a heterocyclic ring selected from the group consisting of:




,

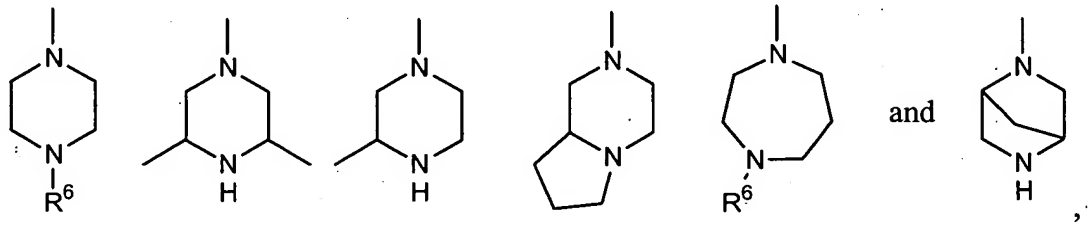
wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl.

15 (Amended). A compound according to claim 1, wherein Ar is a heterocyclic ring selected from the group consisting of pyridinyl, thienyl, imidazolyl, pyrazolyl, benzothienyl, and benzoxadiazolyl, each being optionally substituted with halogen or $C_{1-6}$ alkyl; each of $R^2$ and $R^3$ is H; and [each of] $R^4$ is independently a heterocyclic ring selected from the group consisting of:




, and

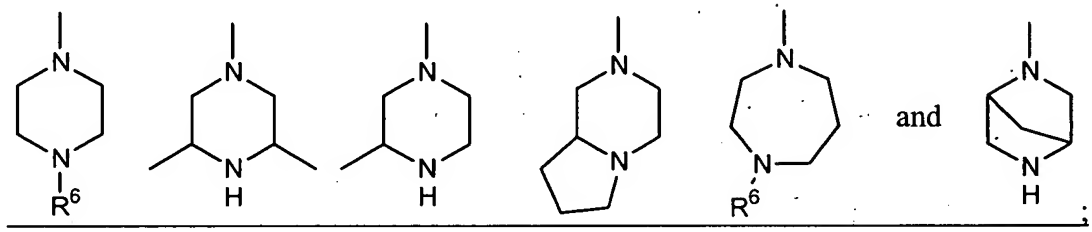
$R^5$ is independently H or a heterocyclic ring selected from the group consisting of:




,

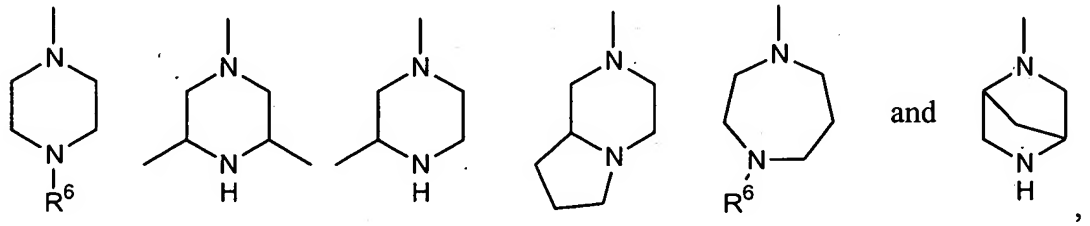
wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl.

16 (Amended). A compound according to claim 1, wherein Ar is 2-pyridyl, 3-pyridyl, or 4-pyridyl; each of $R^2$ and $R^3$ is H; and [each of] $R^4$ is independently a heterocyclic ring selected from the group consisting of:




;

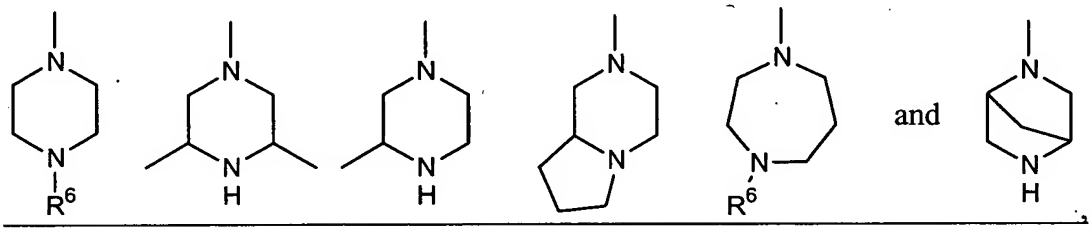
and $R^5$ is independently H or a heterocyclic ring selected from the group consisting of:



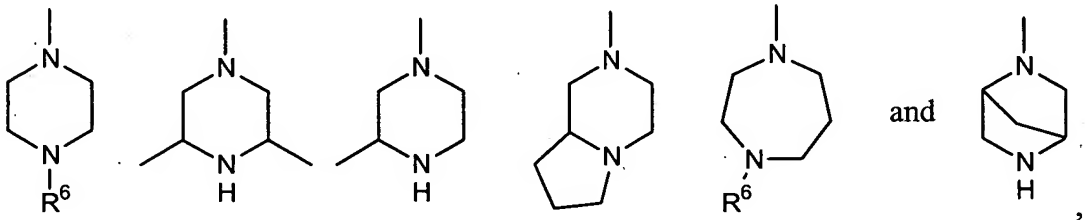

,

wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl.

17 (Amended). A compound according to claim 1, wherein Ar is -$R^9$-phenyl; each of $R^2$ and $R^3$ is H; and [each of] $R^4$ is independently a heterocyclic ring selected from the group consisting of:




, and $R^5$ is independently H or a heterocyclic ring selected from the group consisting of:




wherein $R^6$ is H, $C_{1-3}$ alkyl, or benzyl; $R^9$ is $C_{1-3}$ alkyl or $C_{2-3}$ alkenyl, either of which is optionally substituted with phenyl or phenyloxy; each phenyl being optionally substituted with F, Cl, Br, methyl, $CF_3$, $C_{1-4}$ alkoxyl, $OCF_3$, CN, $NO_2$, phenyloxy, phenyl, methylsulfonyl, or -$NR^7R^8$; and each of $R^7$ and $R^8$ being independently H or $C_{1-6}$ alkyl.

18 (Amended). A compound selected from the group consisting of:

1-phenylsulfonyl-4-piperazinylindole hydrochloride,

1-[(2,5-dimethoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-(mesitylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride,

1-(1-naphthylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride,

N,N-dimethyl-5-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}-1-naphthalenamine hydrochloride,

1-[(4-propoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(2,5-dichloro-3-thienyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(4-methoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(2,4-difluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-([1,1'-biphenyl]-4-ylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(3,4-dimethoxyphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

5-methyl-2-methoxyl-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}phenyl ether hydrochloride,

1-[(2,5-dichlorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(3-chloro-2-methylphenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

2-chloro-5-(4-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}phenoxy)benzonitrile hydrochloride,

4-bromo-2-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}phenyl methyl ether hydrochloride,

4-(1-piperazinyl)-1-(3-pyridinylsulfonyl)-1H-indole hydrochloride,

7-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride,

methyl 2-{[4-(1-piperazinyl)-1H-indol-1-yl]sulfonyl}phenyl sulfone hydrochloride,

1-[(4-fluorophenyl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

1-[(5-chloro-3-methyl-1-benzothien-2-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

4-(4-methyl-1-piperazinyl)-1-(4-methylbenzenesulfonyl)-1H-indole hydrochloride hydrochloride,

4-piperazino-N-(4-trifluoromethyl)phenylsulfonyl)indole hydrochloride,

4-(3-methylpiperazine)-(N-(4-trifluoromethyl)phenylsulfonyl)indole dihydrochloride,

4-(4-methyl-1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(4-ethyl-1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(5-aza-indolizidinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(4-methyl-1-homopiperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(3-methyl-1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(*cis*-3,5-dimethyl-1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(4-isopropyl-1-piperazinyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-((1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptyl)-1-(2-methylbenzenesulfonyl)-1H-indole hydrochloride,

4-(4-methyl-1-homopiperazinyl)-1-(benzenesulfonyl)-1H-indole hydrochloride,

4-(*cis* 3,5-dimethyl-1-piperazinyl)-1-(benzenesulfonyl)-1H-indole hydrochloride,

4-(4-ethyl-1-piperazinyl)-1-(benzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-nitro-benzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-bromo-benzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-chloro-benzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(*E* 2-phenyl-ethensulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(3-trifluoromethyl-benzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-cyanobenzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-chloro-7-chloro-2,1,3-benzoxadiazole sulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(3-cyanobenzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-phenoxybenzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-chlorophenylmethanesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-methylphenylmethanesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(1,1-diphenylethanesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(4-trifluoromethoxybenzenesulfonyl)-1H-indole hydrochloride,

4-piperazinyl-1-(5-[(benzoylamino)methyl]thiophene-2-sulfonyl)-1H-indole hydrochloride,

1-[(N-methyl-1H-imidazol-4-yl)sulfonyl]-4-(1-piperazinyl)-1H-indole hydrochloride,

[N-benzenesulfonyl-5-(4-methylpiperazin-1-yl)-indole,

N-(4-methylbenzenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole,

N-benzenesulfonyl-5-(4-isopropylpiperazin-1-yl)-indole,

N-(4-methylbenzenesulfonyl)-5-(4-isopropylpiperazin-1-yl)-indole,

N-(3,4-dimethoxybenzenesulfonyl)-5-(4-propylpiperazin-1-yl)-indole, hydrochloride,

N-(3-fluorobenzenesulfonyl)-5-(4-propylpiperazin-1-yl)-indole, hydrochloride,

N-(4-propylbenzenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(1-naphtalenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(biphenyl-4-sulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(4-methoxybenzenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(3,4-dimethoxybenzenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(2,4-difluorobenzenesulfonyl)-5-(4-methylpiperazin-1-yl)-indole, hydrochloride,

N-(4-methoxybenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(2,4-difluorobenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(4-butoxybenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(3,4-dimethoxybenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(biphenyl-4-sulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(napthalene-2-sulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(4-propylbenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(3-fluorobenzenesulfonyl)-5-(4-benzylpiperazin-1-yl)-indole, hydrochloride,

N-(4-methoxybenzenesulfonyl)-5-(piperazin-1-yl)-indole, hydrochloride,

N-(2,4-difluorobenzenesulfonyl)-5-(piperazin-1-yl)-indole, hydrochloride,

N-(4-butoxybenzenesulfonyl)-5-(piperazin-1-yl)-indole, hydrochloride,

N-(3,4-dimethoxybenzenesulfonyl)-5-(piperazin-1-yl)-indole, dihydrochloride,

N-(biphenyl-4-sulfonyl)-5-(piperazin-1-yl)-indole, dihydrochloride,

N-(napthalene-2-sulfonyl)-5-(piperazin-1-yl)-indole, dihydrochloride,

N-(4-propylbenzenesulfonyl)-5-(piperazin-1-yl)-indole, dihydrochloride,

N-(3-fluorobenzenesulfonyl)-5-(piperazin-1-yl)-indole, dihydrochloride,

N-benzenesulfonyl-5-(piperazin-1-yl)-indole, dihydrochloride,

3-(1-azabicyclo[2.2.2]oct-2-en-3-yl)-1-[(4-fluorophenyl)sulfonyl]-1H-indole,]

2-iodo-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride,

2-phenyl-1-(phenylsulfonyl)-4-(1-piperazinyl)-1H-indole hydrochloride,

4-piperazinyl-2-methyl-1-benzosulfonylindole trifluoroacetate, and

1-phenylsulfonyl-4-(homopiperazinyl)-indole hydrochloride.

22 (Amended). A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

24 (Amended). A method of treatment [or prophylaxis] of a disease mediated by the serotonin related 5-$HT_6$ receptor comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1.

25 (Amended). A method of treatment [or prophylaxis] of a disease mediated by the serotonin related 5-$HT_6$ receptor comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 18.

#9
Attached

## SECTION I. CNS AGENTS

Editor: David W. Robertson, Pharmacia Corporation
Kalamazoo, MI 49007

# Chapter 1: Same Brain, New Decade: Challenges in CNS Drug Discovery in the Postgenomic, Proteomic Era

Michael Williams^, Joseph T. Coyle#, Sanober Shaikh* and Michael W. Decker**
^Northwestern University School of Medicine, Chicago, IL 60611, #Harvard Medical School, Belmont, MA 02178, *Genset SA, 91030 Evry Cedex, France and **Abbott Laboratories, Abbott Park, IL 60064

Introduction. The brain is a highly complex organ that mediates conceptual thought, cognition, volition, self-consciousness and emotion (1,2). As "the interpreter and responder to environmental challenges", the brain, working via the peripheral nervous system, processes information and controls behavioral responses via "systems replete with specialized circuits, parallel pathways, and redundant mechanisms to protect the individual, thus ensuring propagation of the genome and survival of the species (3,4). Accordingly, brain dysfunction resulting from genetic, environmental and/or aging factors has a major negative impact on the quality of life and individual survival.

## CNS COMPLEXITY AND DRUG DISCOVERY

The human brain contains approximately 100 billion neurons and expresses greater than 60% of known human genes. In comparison, the nervous system of the threadworm, C. elegans, a model system for studying genomic function, has a mere 302 neurons, $3 \times 10^{-6}$ % the number in the human brain. Neurons in C. elegans are interconnected via 600 electrical and 5000 chemical synapses (5). The C. elegans genome codes for approximately 1000 G-protein coupled receptors (GPCRs), 90 ligand-gated ion channels, 80 potassium-selective ion channels and 228 nuclear receptors providing a virtually infinite number of postgenomic molecular substrates through which neuronal function can be regulated (6,7). Understanding this complexity at the level of the human brain and postgenomic interactions between genes and their products (epigenetics; 8) is a key challenge in understanding human CNS disease pathophysiology and in designing new drugs that are safer and more efficacious to treat these diseases.

The characterization of simpler systems like C. elegans, has prompted a shift away from an increasingly reductionistic approach to the study of the brain and nervous system, focused almost exclusively on molecular function at the synaptic level, to a renewed appreciation of the hierarchical complexity (gene, synapse, pathway, phenotype) of the nervous system (9) and the need to: a) integrate structure with function at the tissue and whole animal level; and b) integrate and iterate animal studies with emerging clinical research at both the systems and compound levels. Given emerging knowledge regarding the intrinsic complexity of the human brain, the success resulting from serendipity in the last 40 years is impressive and has provided a number of highly effective CNS drugs, the majority of which act synaptically, either mimicking (agonists), facilitating (transmitter uptake blockers, allosteric modulators) or antagonizing the effects of endogenous neurotransmitters and neuromodulators (10,11). Not only neurons but also glial cells - astrocytes, microglia, etc. are potential drug targets.



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The function of the brain is extremely dynamic. Neonate, adult and aged brains are morphologically and phenotypically very distinct. Diseased brain can be very different from the 'normal', healthy brain. Transmitters and receptors present during development disappear in adult brain, while receptors change in number and function due to disease and nervous system trauma. Mechanisms to sustain brain homeostasis, including trophic factor maintenance of neuronal viability, are negatively impacted by aging, leading to an accumulation of environmental insults. Brain function is influenced by hormones, via the hypothalamic-pituitary axis (HPA; 3) and by peripheral e.g. cardiovascular/ vascular, system function.

Global sales of CNS drugs in 1999, including pain, exceeded $50 billion, approximately 15% of the total global drug sales. This market will continue to grow as the aging population increases (by 2030, the number of Americans 65 or older will double; 11) and life-style factors, including stress and information overload resulting from a breakdown in societal support systems for the individual (3,12,13).

The Decade of the Brain initiative of the 1990s was intended to "enhance the awareness of the benefits to be derived from brain research" and thus elucidate the cause(s) of CNS disorders, enabling development of effective treatments (14). Despite this and newer drug discovery technologies, both chemical and biological, that include draft sequences of the human genome (15), the discovery and timely development of CNS drugs remains one the most challenging in pharmaceutical research (11). Factors contributing to this include: the inherent complexity of the brain; a paucity of knowledge regarding function at the molecular level - especially in disease states; animal models with limited predictive value; a lack of robust, quantitative diagnostic tools to track disease occurrence and progression; imprecise physician diagnoses of symptomatically related psychiatric disease states that frequently involve ethnic and cultural factors; and challenges in defining efficacy in human trials due to high placebo responses (16,17).

CNS drug discovery to date has thus been highly iterative in nature, building on established mechanism(s) of action of clinically effective compounds with improvements in tolerance and/or safety. The successful antidepressant SSRIs (selective serotonin reuptake inhibitors), e.g., fluoxetine, are mechanistically similar to the traditional tricyclic antidepressants (TCAs), e.g. impramine. In addition, the reason for the superior efficacy of the 'atypical' antipsychotic medication, clozapine – the mechanism(s) of action of which has been repeatedly redefined as new CNS receptors have been identified – as compared with other dopamine (DA) receptor antagonists, has not been elucidated.

An additional complication in developing new CNS drugs is that drugs currently used for one indication can be used to treat different CNS disorders - e.g. valproate for epilepsy, bipolar affective disorder (BPAD), migraine (18) and dementia-associated agitation, and anticonvulsants, e.g. gabapentin, that modulate neuronal firing are used for the treatment of neuropathic pain and, potentially, BPAD.

Diagnosis and classification of CNS disorders relies on two key reference works: the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ Edition (DSM-IV) and the International Classification of Diseases - Revision 10 (ICD-10), the European equivalent of DSM-IV. While invaluable tools, their use is confounded by ethnic -, societal - and gender- related differences in patient diagnosis. CNS diseases also have a high incidence of co-morbidities - depression is associated with chronic pain and excessive stress and alcoholism with depression, anxiety and cognitive impairment. The neuronal loss associated with stroke leads to cognitive dysfunction, mood disorder(s) and

TABLE 1: TRENDS IN PSYCHIATRIC DRUG TREATMENT

| Disease State | Current Approaches | Experimental Approaches |
|---|---|---|
| **Schizophrenia** | DA receptor blockers – haloperidol, clozapine, chlorpromazine, risperidone, olanzepine | DA: Clozapine-like agents, partial agonists, D4 receptor antagonists. NMDA receptor/glycine modulators - D-serine, serine racemase α-7 nicotinic receptor agonists $5HT_{2A}$ inverse agonists – AC 90179 Neurokinin-3 and cholecystokinin$_1$ antagonists |
| **Depression** | TCAs - impramine, amitriptyline: Monoamine oxidase inhibitors (MAOIs) - tranylcypromine SSRIs- citalopram, fluoxetine SNRIs (5HT/ NE reuptake inhibitors) - venlafaxine | Improved monoamine uptake inhibitors $5HT_{1A}$ receptor ligands NK-1 receptor antagonists Corticotropin releasing factor (CRF) receptor antagonists |
| **Bipolar Affective Disorder** | Lithium, valproic acid, carbamazepine | Antiepileptics: pregabalin, topiramate etc. Valproate analogs - TV-1901 etc. |
| **Anxiety:** panic disorder, OCD (obsessive-compulsive disorder) GAD (generalized anxiety disorder), PTSD (postraumatic stress disorder), acute stress disorder | Benzodiazepines (BZs)- diazepam, clonazepam $5HT_{1A}$ partial agonists- buspirone SSRIs | Newer BZs: pagaclone, deramciclane $5HT_{1A}$ agonists: lesopitron, S-15535 Orphanin FQ receptor agonists – Ro 64-6198 CRF receptor antagonists |
| **Attention deficit hyperactivity disorder (ADHD)** | Psychostimulants – methylphenidate d-amphetamine | α4β2- nicotinic receptor agonists – ABT-089 Histamine $H_3$ antagonists - GT 2331 Monoamine uptake blockers - atomoxetine |
| **Compulsive/addictive disorders :** cocaine, amphetamine, heroin, alcohol, nicotine (smoking) addiction Recreational drug use Cannabinoid, PCP Compulsive disorders: Gambling, sexual behavior, eating (obesity, anorexia, bulimia) | Methadone, LAAM Naloxone Disulfiram Acamprosate Nicotine patches Buproprion Phenylpropanolamine Sibutramine Orlistat PPARγ antagonists - troglitazone | DA transport blockers - RTI -113 D1 receptor ligands - DAS-431, CEE 03-310 Cocaine vaccine (TA-CD) and catalytic antibodies - mAb 15A10 Obesity: Leptin modulators, CART, GLP1, amylin, galanin, neuropeptide Y, α- MSH, famoxin, fatty acid synthase (FAS) inhibitors, orexin, melanocortin - 4 (MC-4)/SLC-1 and SOCS3 antagonists |
| **Sleep disorders:** sleep pattern disruption (jet lag) Insomnia, narcolepsy | Hypnotics- Secobarbital, triazolam, estazolam Modafinal, Melatonin | Agomelatine, Adenosine agonists $H_3$ agonists – SCH 50971 Orexin agonists, NBI 34060 |
| **Sexual disorders** Erectile dysfunction/ Female sexual dysfunction | Sildenafil Apomorphine | IC-531, BAY 38-9456 DA agonists |

dementia; and the loss in cognitive function occurring in Alzheimer's disease (AD) leads to aggression, anxiety and depression. The overlap in symptoms between diagnostically distinct disease states and the high co-morbidity with other distinct CNS disorders mak s clinical experimentation an absolute necessity in defining the utility of CNS drugs. The area is historically replete with compounds advancing to the clinic for on indication and being found to be useful for another (10).

## TARGET DYNAMICS

Ongoing research, basic and applied, has continued to identify a number of new approaches to the treatment of CNS disorders that are currently to or through clinical trial validation. These are shown alongside existing approaches in Tables 1 and 2; some are incremental improvements on existing mechanisms (D4 antagonists for schizophrenia; valproate analogs) while others (D-serine for schizophrenia (19); caspase inhibitors for neurodegenerative disorders; vaccines for AD and stroke (20,21)) are highly novel approaches. In many instances however, the challenge in CNS drug R & D is in improving (reducing) the side effect liabilities for compounds active at a known CNS drug target (e.g. D2 receptor) to allow higher levels of drug to be administered. This can be accomplished by understanding the mechanism(s) by which known compounds produce their side effects and by then 'tuning out' this property or adding additional properties to newer compounds to overcome side effects. Side effects, while never a trivial issue, are of increasing importance, especially in CNS disorders requiring chronic therapy in a young population that is, apart from their disease-related disability, relatively healthy. For example, antipsychotics show a class-related phenomenon of QT-syndrome prolongation that can result in ventricular tachycardia, heart block and fatalities. This has been a major factor in the comparative lack of new drug approvals for this class (22).

A less obvious instance of potential side effect liability results from approaching the process of compound identification using a highly reductionistic molecular approach that lacks an integrated, pharmacological framework. The logic, a priori, is that by identifying a compound interacting with high affinity at a defined molecular target, it will lack interactions with other molecular targets. Leptin, the 167mer secreted from adipocytes, acts via leptin receptors to reduce food intake and was thought to represent a promising anorectic agent (23) However, acting via the hypothalamus, leptin also inhibits bone formation, an effect that would limit the chronic use of the peptide in obesity (24).

## EXPLOITING THE GENOME OF THE BRAIN

A large number of chromosomal loci containing susceptibility genes potentially involved in disease etiology as well as gene candidates for schizophrenia, BPAD, etc. have been identified (25,26). Validation of these is based on epidemiological data showing a significant genetic contribution to disease etiology. Interactions between more than one susceptibility gene and environmental risk factors (the "envirome"; 27) clearly contribute to disease incidence, the norm of reaction factor - indicating that biology – and human behavior - cannot be classified simply in terms of DNA sequences (28). In schizophrenia, concordance rates between monozygotic and dizygotic twins are 50% and 15% with an overall heritability of 68% (29). Focusing on disease genes within chromosomal regions implicated through genetic linkage analysis (using DNA from affected family pedigrees) requires a case control study design involving large cohorts (200-500 of patients and controls) derived from ethnically homogeneous populations matched for age and sex. The quality of the case histories is crucial in assuring the validity of diagnosis and in identifying ethnically unmatched individuals who contribute to stratification effects. The identification of putative disease-associated genes in an initial population should be replicated in additional populations. However, gene association studies often fail to replicate due to locus or genetic heterogeneity or simply because of the poor quality of the collection. With the sequencing of the human genome and identification of more than 2.5 million single nucleotide polymorphisms (SNPs; 30), phenotypic traits will be increasingly correlated with genetic variability with the

TABLE 2: TRENDS IN NEUROLOGICAL DRUG TREATMENT

| Diseas State | Current Appr aches | Experimental Approaches |
|---|---|---|
| **Dem ntias** AD; early onset familial AD (EOFAD), vascular dementia, dementia with Lewy bodies (DLB), dementia associated with Parkinson's disease, AIDS and age-related dementia. Picks' dementia, frontotemporal, substance-induced and alcohol dementia | Cholinergic replacement: Donepezil, rivastigmine Galanthamine etc. Nootropics: piractetam, aniracetam idebenone | Inhibitors of oxidative stress: MAO-B inhibitors - rasagiline; free radical scavengers: ARL-16556<br>Nicotinic and DA D1/D5 agonists.<br>COX-2 inhibitors – rofecoxib<br>HMG CoA reductase inhibitors – simvistatin<br>Trophic factor replacement /neuronal growth stimulators – BDNF, AIT-082, kinase signaling pathways<br>Amyloid vaccine - AN 1792/Betabloc<br>BACE1 inhibitors - L-685,458<br>Caspase inhibitors – IDN-6556 |
| **Parkinson's disease (PD)** | DA replacement: L-dopa, pramipexole cabergoline, piribedil, pergolide, ropinerole | Neuroimmunophilins, GPI-1337<br>Adenosine $A_{2A}$ agonists - KW 6002, SCH 58261<br>Inhibitors of oxidative stress: Rasagiline - Caspase inhibitors |
| **Epilepsy** | Phenytoin, carbamazepine, valproate, ethosuximide, Phenobarbital Felbamate, lamotrigine, gabapentin, tiagabine, Vigabatrin | Leviracetam . Valproate analogs: TV-1901, NPS 1776, ABS-103, DP-VPA etc. Sodium channel modulators: GW 273293, Co 102862<br>Calcium antagonists: zonisamide, retigabine, PNU 156654E<br>GABA modulators: losigamone, pregabalin, Co 15279, rufinamide.<br>Glutamate receptor antagonists: Talampanel , TV 141, PNU 191779E |
| **Stroke** | tissue plasminogen activator, tPA | NMDA/ glycine site modulators: D-serine, licostinel, MDL 105518, GV 224029<br>NR1 vaccine (AAVNMDAR1)<br>NAALADase inhibitors: 2-PMPA<br>Caspase-3 inhibitors<br>$P2X_7$ receptor antagonists<br>$P2Y_{12}$ antagonists: AR-C 69931MX |
| **Spinal cord injury** | Steroids | NR2B NMDA antagonist - CP-101,606 |
| **Multiple sclerosis** | Interferon<br>Immunosupressants<br>methylprednisolone<br>prednisone<br>methotrexate<br>azathioprine | Clabridine, mitoxantrone, paclitaxel, sulfasalazine, lenercept (sTNFR-IgG p55)<br>ISIS 107248 - antisense<br>Cannabinoid receptor agonists: R (+)-WIN 55,212, methanadamide |
| **Pain** | Opioids<br>NSAIDs<br>COX-2 inhibitors | $\alpha 4\beta 2$ nicotinic agonists – ABT-594<br>NMDA receptor antagonists<br>Neurokinin-1 antagonists<br>Vanilloid receptor modulators<br>$P2X_3$ receptor antagonists<br>$GABA_B$ activated Kirs – gabapentin<br>Voltage-gated $Na^+$ channels<br>Growth factors – NGF |

information generated used to substantiate emerging findings that genes associated with one CNS disease may also be associated with other distinct disease states e.g. disease A involves interactions between genes X, Y and Z (plus the "envirome"; 27) while disease B involves genes X, S and T. Currently used symptomatic approaches to disease diagnosis may be replaced with patient genotyping followed by the use of compounds targeted towards the products of the individual disease